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Severe chronic bronchiolitis as the presenting feature of primary Sjögren's syndrome

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Summary
Sjögren's syndrome is a frequent auto-immune disorder with a pulmonary location in almost 10% of the patients. Although bronchial involvement is very common, most patients only complain of cough and this involvement rarely results in severe symptoms or chronic respiratory failure are rarely observed.

We describe here 5 patients with severe chronic bronchiolitis revealing primary Sjögren's syndrome. The lung involvement resulted in chronic bronchorrhea, recurrent sinusitis, diffuse bronchiolar nodules with bronchiectasis on the CT scan, and a severe obstructive airway pattern on lung function tests. Improvement was obtained in 4 patients with combination of inhaled corticosteroids, inhaled long acting beta-agonists, and a low dose of erythromycin.

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Introduction

Sjögren's syndrome is an auto-immune disease characterized by a lymphocytic infiltration of the exocrine glands. Sjögren's syndrome can occur alone (primary Sjögren's syndrome), or in association with other auto-immune diseases (secondary Sjögren's syndrome). The most frequent manifestations are an asthenia and a sicca syndrome with a xerostomia and a xerophtalmia. Twenty to 40% of the patients may also have an extra-glandular organ manifestation.[1,2] The prevalence of a lung is not clearly established, varying from 9 to 90% of the patients, according to the procedure performed for evaluation. However, clinically significant lung involvement occurs in 9% of the patients in recent series of patients with a primary Sjögren's syndrome.[3,4] Although all parts of the respiratory system may be involved,[5] airways involvement is very frequent in Sjögren's syndrome and affects both upper and lower airways. An infiltration of airways wall with inflammatory cells, particularly lymphocytes and plasmocytes, is detected in half of the patients with a Sjögren's syndrome.[6] A follicular bronchiolitis and a lymphocytic bronchiolitis are the most common forms of bronchiolar involvement.[2] Regarding functional abnormalities, the bronchiolar involvement has been mostly described as a reduction of airflow indexes, such as decreased MEF_{50} and MEF_{25}, and has been observed in up to 90% of the patients with a Sjögren's syndrome.[7] Almost half of the patients may also have a bronchial hyperreactivity.[8] On CT scans, a bronchial thickening is observed in 8%—22% of the patients and bronchiolar nodules are observed in 6%—24% of the patients.[7,9,10]

Despite the high frequency of pathological or radiographical defined bronchiolar disorders in Sjögren's syndrome, a severe clinical involvement of the airways rarely occurs and the diagnosis of a Sjögren's syndrome in patients with chronic bronchiolar disorders is very rare.[7,11]

We describe here 5 patients who presented a severe bronchiolitis associated to a chronic respiratory failure revealing a primary Sjögren's syndrome.

Methods

This is a retrospective, observational, non-interventional study. Patients were recruited in two university pneumology departments with a special interest in Sjögren's syndrome (Bichat Hospital and Saint Louis Hospital) and in a French center commonly in charge of Sjögren's syndrome (Rheumatology department, BicêtreHospital). We identified all patients diagnosed with a Sjögren's syndrome that was revealed by a chronic bronchiolitis. To be included, the patients had to present clinical signs of a severe bronchiolitis, diffuse bronchiolar nodules evidenced on a CT scan and at least one of the following objective criteria of primary Sjögren's syndrome: a salivary lymphocytic infiltration of the salivary glands with a Chisholm score ≥ 3 or the presence of anti-SSA or anti-SSB antibodies. Exclusion criteria at diagnosis were : a definite connective tissue disease other that Sjögren's syndrome, AIDS, a sarcoidosis, a graft versus host disease, a past head and neck radiation therapy, a hepatitis C infection and a concomitant use of anticholinergic drugs.

The clinical charts of the patients were reviewed and the following items were analyzed: age at diagnosis, age at onset of the first symptoms, gender, history of persistent purulent rhinosinusitis, smoking history, history of childhood respiratory infections or pulmonary tuberculosis, atopy or asthma, connective tissue disorders, symptoms of gastroesophageal reflux, infertility, and familial history of immunodeficiency or pulmonary sepsis. Lung function tests at diagnosis and during the follow-up were recorded. Outcome data were recorded until death or the last scheduled visit.

All available high resolution computed tomographies (HRCT) of the thorax were centrally reviewed by an experienced chest radiologist (MPD). A lesional score was given using a semi-quantitative grading system.[12] A score from 0 (no lesion) to 3 was attributed to each lobe and to each lingula and culmen. The maximum theoretical score was then 18.

Data were collected on a standardized and anonymous collection form. For this retrospective, observational, non-interventional analysis of medical records, French authorities do not require a specific approval of an Internal Review Board or the consent of the patients. Data are reported as median [extremes].

Case reports

Bichat and Bicêtre hospitals databases retrieved 101 patients with primary Sjögren's syndrome associated to a "pulmonary disease". After review, only 4 patients fulfilled the inclusion criteria. One additional patient was referred by Saint Louis hospital, without the use of a database. Patients were 4 women and 1 man. The median age at diagnosis was 58 years [38—70]. All patients presented with a prominent dyspnea lasting from 1 to 144 months (median 10 months) at the time of diagnosis associated to a cough and chronic sputum for 4 of them (Fig. 1). Four patients had required a chronic nasal oxygen therapy at the time of diagnosis because of a severe chronic hypoxemia (Fig. 1). Three patients had declared a history of repeated upper airway infections lasting since 1—14 years. Lung sounds were always abnormal for all patients. No patient had received anticholinergic drug.

For each patient, a lung CT scan (Figs. 1 and 2) had evidenced diffuse and profuse centrilobular micronodules associated with mild bronchiectasis. Alveolar consolidations had been detected at diagnosis in 3 patients, and disappeared on further CT scans, as patients were treated with antibiotics and physiotherapy. For 4 of the patients, a sinus CT scan had revealed a sinusitis without osteolytic lesion.

In all patients, the pulmonary function tests had evidenced an obstructive pattern, defined as a reduced FEV_1/FVC ratio $<70\%$, in all the patients (Table 1).

Bronchial aspirates had grew with *Pseudomonas aeruginosa* in one patient, and with *Staphylococcus aureus* in one other patient. Mycobacterial and fungal cultures were negative for all patients. Broncho-alveolar lavage was performed in 4 patients and revealed an increased cellularity (950 cells/mm^3 [500—25400]) with prominent neutrophilia (80% [39—100]).

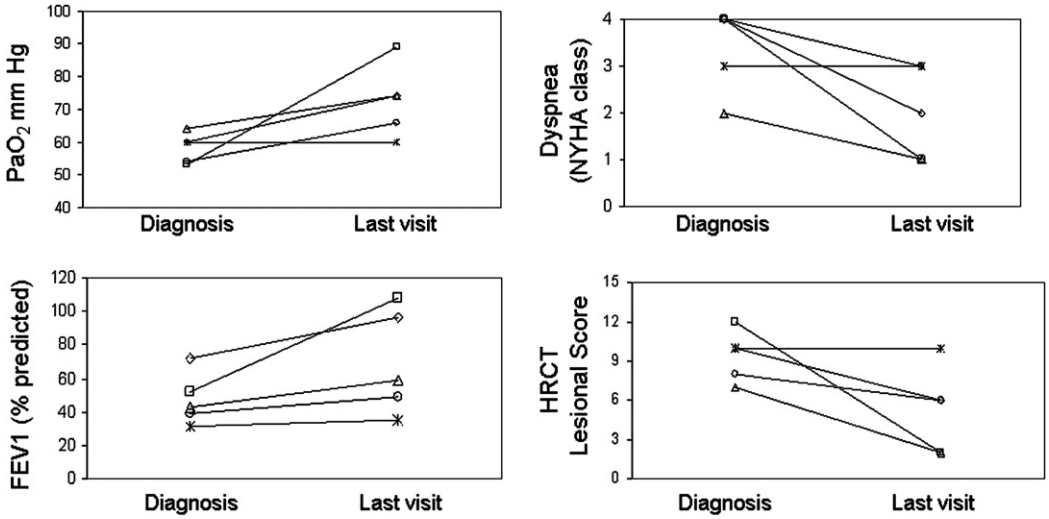

Figure 1 Evolution of PaO_2, dyspnea, FEV_1, and CT lesional score of the five patients from diagnosis to the last follow-up visit. Dyspnea was assessed using NYHA scale. Lesional score was defined according to Taouli et al.[12] Among the 5 patients, 4 were improved on all criteria analyzed.

A surgical lung biopsy had been performed in one patient at the time of surgery for thymoma. Respiratory failure was considered too severe for the 4 other patients to perform a surgical lung biopsy.

For all patients, common etiologies of chronic bronchiolar disorders had been ruled out: serum immunoglobulins levels were normal or increased; α1-antitrypsin levels; the search for cystic fibrosis was negative and the ciliary motility on nasal mucosa biopsy was normal. None of the patients had declared a history of childhood respiratory infections (pertussis, pneumonia, or measles), or a history of pulmonary tuberculosis. None of the patients had an evidence of an inflammatory bowel disease, or a yellow nail syndrome.

All 5 patients were considered as having a primary Sjögren's syndrome according to the Fox criteria[13] and 4 of them according to the tree procedure of the revised American—European Consensus Group criteria (AECC) (Table 2).[14] Four patients had extra-glandular manifestations of their Sjögren's syndrome. None of the patients had other definite connective tissue disorder. All patients had positive antinuclear antibodies. Anti-SSA antibodies were present in 2 patients. Other auto-antibodies were less frequently detected.

The median follow-up was 78 months [35—106]. All patients had been treated with inhaled corticosteroids and long acting beta-agonists associated with chest physiotherapy to improve the drainage of the bronchial secretions. Three patients had been treated with erythromycin (500 mg/d). Three patients had been dramatically improved with their therapy and weaned from oxygen therapy (Fig. 1).Three patients had recurrent respiratory infections during follow-up, and one of them had died from pneumonia.

Patient 1 (Fig. 1, diamond)

Patient 1 was a 58-year-old woman, 60 year-pack former smoker. She presented with a dyspnoea and chronic expectorations since 1 year. She also presented arthralgias,

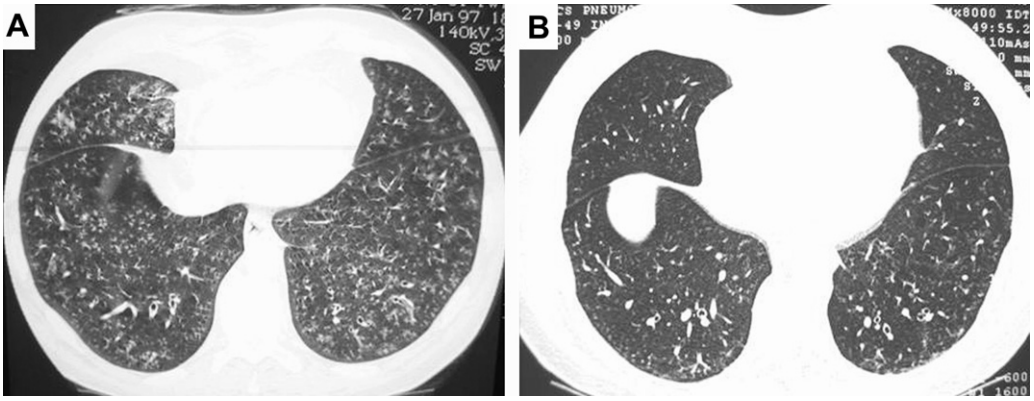

Figure 2 CT scans of the chest from patient 4 from diagnosis (A), to the last CT scan of follow-up visit (B), 76 months later. A dramatic clinical improvement was noted 6 months after the initiation of erythromycin therapy followed by impressive radiographical attenuation of bronchiolar micronodular lesions.

Table 1 Pulmonary Function Tests at diagnosis of five patients with severe bronchiolitis and primary Sjögren's syndrome. Data are expressed as measured values and percentage (CECA 1993[27]).

Patient	TLC L (%)	RV L (%)	FEV_1 L/s (%)	FEV_1/FVC ratio	MEF 75, 50, 25 L/s (%)	DLCO mmol/min/kPa (%)	PaO_2 at rest (mmHg)	$PaCO_2$ at rest (mmHg)
n°1	7.23 (140%)	3.6 (195%)	1.89 (72%)	0.64	2.52, 1.09, 0.25 (45, 28, 17%)	2.06 (32%)	60	43
n°2	2.83 (82%)	1.51 (100%)	1.14 (39%)	0.52	0.59, 0.46, 0.13 (10, 11, 7%)	NA	73	37
n°3	2.71 (64%)	1.28 (70%)	0.66 (43%)	0.59	1.43, 0.63, 0.10 (30, 10, 10%)	3.35 (52%)	64	40
n°4	8.84 (108%)	4.03 (159%)	2.13 (52%)	0.44	1.84, 0.65, 0.14 (22, 12, 6%)	3.42 (30%)	53	40
n°5	2.56 (70%)	1.61 (100%)	0.51 (31%)	0.6	0.50, 0.22, 0.12 (10, 7, 11%)	NA	60	42

associated to oral and ocular symptoms and ocular signs. Sjögren's syndrome was confirmed by histopathology. She also presented an auto-immune hepatitis and thyroiditis. Pulmonary function tests revealed an irreversible obstructive pattern with a pulmonary distension. A CT scan revealed lower lung zone predominant micronodules, with limited bronchiectasis and maxillary sinusitis. Broncho-alveolar lavage revealed 500 cells/mm^3, with 88% of neutrophils without any pathogen. A cystic fibrosis was excluded by normal sweats chloride testing.

She was treated with low dose of prednisone and azathioprine for her by auto-immune hepatitis. After 36 months of follow-up, she presented a dramatic improvement (the PaO_2 increased from 60 to 74 mm Hg) with only one respiratory exacerbation secondary to *S. maltophilia* infection.

Patient 2 (Fig. 1, triangle)

Patient 2 was a non-smoker 30 year old woman. She presented with a dyspnoea and chronic expectorations since 14 years. She also presented with arthralgias, a Raynaud phenomenon, oral and ocular symptoms and ocular signs, Sjögren's syndrome was confirmed by histopathology. The antinuclear antibodies were at 1/1280 without specific auto-antibodies. Pulmonary function tests revealed an irreversible obstructive pattern with increase ratio RV/TLC (residual volume/total lung capacity). CT scan revealed micronodules with upper lobes predominance, with limited bronchiectasis and a maxillary sinusitis. Bronchial aspirates grew with pseudomonas aeruginosa. Cystic fibrosis was excluded by normal sweats chloride testing, normal transepithelial nasal potential difference, and absence of the 31 main mutations of CFTR. The ciliary motility was normal on nasal mucosa biopsy.

She was treated with erythromycin during 18 months and azithromycin during 10 months with a partial improvement. During the 96 months of follow-up she presented 2 to 3 respiratory infections per year. Repeated sputum analysis grew with *E. Coli* and *H Influenza*.

Patient 3 (Fig. 1, circle)

Patient 3 was a non-smoker 70-year-old woman. She was treated for ischemic cardiopathy. She presented with a dyspnoea since 1 year. She also presented with oral and ocular symptoms and ocular signs. Sjögren's syndrome was confirmed by the presence of anti-SSA antibodies. Pulmonary function tests revealed a reversible obstructive pattern mixed with restrictive pattern. CT scan revealed pulmonary peripheral micronodules, with limited bronchiectasis and a maxillary sinusitis. Broncho-alveolar lavage revealed 700 cells/mm^3, with 39% neutrophils, without any pathogen. A cystic fibrosis was excluded by normal sweats chloride testing, normal transepithelial nasal potential difference, and the absence of the 31 main mutations of CFTR. The ciliary motility was normal on the nasal mucosa biopsy.

Beta-blockers were withdrawn with a partial improvement after a follow-up of 78 months. There was no respiratory exacerbation but the patient suffered from recurrent myocardial infarction.

Patient 4 (Fig. 1, square)

Patient 4 was an 8 pack-year former smoker, 58-year-old man. He had received a mediastinal radiotherapy for a Hodgkin's disease, 19 years before diagnosis. He was considered as cured from his Hodgkin's disease. He presented with a dyspnoea and chronic expectorations since 13 year. He also presented with arthralgia and oral symptoms. Sjögren's syndrome was confirmed by the presence of anti-SSA antibodies and by histopathology. Pulmonary function tests revealed a severe irreversible obstructive pattern. CT scan revealed diffuse pulmonary micronodules and a pansinusitis (Fig. 2). Broncho-alveolar lavage revealed 950 cells/mm^3, with 83% neutrophils, without any pathogen. A cystic fibrosis was excluded by normal sweats chloride testing, normal transepithelial nasal potential difference, and the absence of the 31 main mutations of CFTR. The ciliary motility was normal on the nasal mucosa biopsy.

He experienced 3 respiratory infections in the first 6 months of follow-up without any identified pathogen. A chronic sinusitis required surgical maxillary drainage. The patient received erythromycin (500 mg/day) during 76 months with a dramatic improvement (Fig. 1). He developed a diffuse large B cell lymphoma after 36 months of follow-up, treated with chemotherapy and an autologous

Table 2 Clinical and laboratory parameters at diagnosis of five patients with severe bronchiolitis and primary Sjögren's syndrome [14].

Patient	Age	Extra-pulmonary symptoms	Other auto-immune disease	Ocular symptoms	Oral symptoms	Ocular signs (Schirmer's test)	Histopathology: Chisholm score	Gammaglobulinemia (g/L)	Auto-Antibodies		
									Antinuclear titer	SSA or SSB	Other auto-antibodies
1	58	Arthralgia	Hepatitis Thyroiditis	yes	yes	yes	4	19	1/1600	Absence	Anti-smooth muscle, anti-thyroglobuline, anti-peroxidase
2	30	Arthralgia Raynaud phenomenon	no	yes	yes	yes	3	17	1/1280	Absence	no
3	70	no	no	yes	yes	yes	1	12	1/640	SSA	no
4	45	Arthralgia	no	no	yes	no	3	9.4 with monoclonal IgMKappa (<2 g/l)	1/2560	SSA	Rheumatoid factor
5	61	no	Thyroiditis Myastenia gravis	yes	yes	no	3	12.2	1/2560	Absence	Anti-thyroglobuline, anti-peroxidase, anti cardiolopin, anti-acetylcholine receptor

stem cell transplantation. After a total of 106 months of follow-up he is still in remission of bronchiolits and lymphoma.

Patient 5 (star)

Patient 5 was a non-smoker 61-year-old woman. A thymoma was diagnosed concomitantly to a chronic bronchiolitis. She presented with a dyspnoea and expectorations since 7 years. She also presented with oral and ocular symptoms. Sjögren's syndrome was supported by a salivary glands histopathology. She also presented with myasthenia gravis and auto-immune thyroiditis. Pulmonary function tests revealed an irreversible obstructive pattern mixed with restrictive pattern. CT scan revealed peripheral micronodules, with limited bronchiectasis and pansinusitis. Broncho-alveolar lavage revealed 2500 cells/mm^3, with 100% neutrophils, without any pathogen. A cystic fibrosis was excluded by normal sweats chloride testing, a normal transepithelial nasal potential difference, and absence of the 31 main mutations of CFTR.

Lung surgical biopsies, performed at the time of the thymoma surgery, evidenced a cellular bronchiolitis characterized by a peribronchiolar lymphoplasmacytic infiltration. She did not received any specific treatment for her bronchiolitis during 60 months. She was referred to Bichat hospital because of a severe lung function alteration and recurrent respiratory infections. She died from sepsis after 4 months of erythromycin, probably due to a *Pseudomonas pneumonia*.

Discussion

This report describes 5 patients with a severe obstructive lung disease consistent with a chronic bronchiolitis, in whom the bronchial disease led to the diagnosis of a Sjögren's syndrome. Although some degree of histological or radiographical bronchiolar involvement is common in patients with a primary Sjögren's syndrome, this clinical syndrome has not been previously individually described, despite a potential improvement with therapy.

We believe that the diagnosis of primary Sjögren's syndrome was assesed in these 5 patients. All of them fulfilled the Fox criteria for probable primary Sjögren's syndrome.[13] Four of the 5 patients fulfilled the tree procedure of AECC criteria.[14] The fifth patient did not fulfil this procedure, because an objective evaluation of salivary gland function had not been performed. However this patient had oral and ocular symptoms associated with a histopathology score of 3 and elevated antinuclear antibodies titer (1/2560), that reinforced the diagnosis of a probable Sjögren's syndrome. Indeed the sensitivity and specificity of the AECC classification tree are 96.1 and 94.2% respectively, the clinical judgement of an experimented observer is still considered as the gold standard for the diagnosis of Sjögren's syndrome [14]. Patient 4 had received mediastinal radiotherapy 19 years before the diagnosis of Sjogren's syndrome. Sicca syndrome may be a long-term side effect of mediastinal radiotherapy. However the patient 4 also had arthralgias, a positive rheumatoid factor, high level of antinuclear antibodies with anti-SSA

specificity, and lymphocytic infiltration of salivary glands (Chisholm score at 3) making the diagnosis of Sjögren's syndrome highly probable.

All the patients presented with typical centrilobular micronodules on the CT scan (Fig. 2) and a severe obstructive pattern on lung function tests, indicating a bronchiolar disorder. Normally, bronchiolitis should have been confirmed by an histological proof. Even if the severity of the respiratory insufficiency did not aloud a surgical lung for 4 of the patients, it was performed in one patient and a cellular bronchiolitis was diagnosed.

We believe that the bronchiolar disorder observed in these patients is not fortuitous but directly linked to primary Sjögren's syndrome. Indeed alternative etiologies of bronchiolitis have been ruled out in every patient by experienced pulmonologists. Furthermore mild bronchiolar abnormalities have been consistently detected in patients with a Sjögren's syndrome. Several studies have evidenced a mild airway obstruction in patients with a Sjögren's syndrome[7,15–17] and in series of Sjögren's syndrome patients without respiratory complaints, CT scans evidenced bronchiectasis in 5–46% of the patients[10,18] and centrilobular micronodules in 6–29% of the patients.[7,9,12] We still have poor data regarding the morphology of the airways in Sjögren's syndrome. Bronchial biopsies showed an increased number of CD4 positive T lymphocytes in the proximal airways.[6] Transbronchial lung biopsies[17,19] and surgical lung biopsies[2,20] both showed a peribronchiolar and an interstitial inflammation. Two main bronchiolar histological subtypes have been described in Sjögren's syndrome patients: a lymphocytic bronchiolitis without follicles formation seems to be the most frequent abnormality,[20,21] whereas a follicular bronchiolitis, more or less associated with a lymphoid interstitial pneumonia, is rare.[19,22] A diffuse panbronchiolitis has been described in one Japanese patient.[23] A constrictive bronchiolitis does not seem to be a feature of Sjögren's syndrome.

Despite the frequency of a bronchiolar involvement in Sjögren's syndrome, usually bronchial involvement does not induce a severe clinical syndrome. Most patients only suffer only from dry cough.[7] This makes our series of patients highly original as it demonstrates that an airway involvement can be responsible for a severe chronic bronchopulmonary failure in patients with a Sjögren's syndrome. Furthermore this study demonstrates that a chronic bronchiolitis may reveal a Sjögren's syndrome. Among the connective tissue diseases, bronchiolitis has been reported mostly in rheumatoid arthritis,[24] and exceptionally in systemic sclerosis,[25] and lung involvement may precede the diagnosis of rheumatoid arthritis, although this rarely occurs (12% of patients in a recent series).[24]

Interestingly, recurrent infections of the upper respiratory tract were a key feature in 4 out the 5 patients studied. Recurrent infections of the upper and lower respiratory tracts are known manifestations of Sjögren's syndrome.

Our data indicate that a specific therapy may be of value in a Sjögren's syndrome associated to a bronchiolitis. Here, one patient improved with erythromycin and one other patient with an immunosuppressive therapy (corticosteroids and azathioprine). We do not believe that the bronchiolitis would have spontaneously improved in our patients, as no patient was cured after 6 months of follow-up. Furthermore, patient 5 did not receive any therapy during the 76 months proceeding the diagnosis and no spontaneous improvement (CT, functional or clinical) occurred. Only few data exist on the effect of therapy on a bronchiolitis in Sjögren's syndrome. We believe that a therapeutic trial with macrolides should be performed in patients with a symptomatic bronchiolitis in the context of a Sjögren's syndrome as it could be successful. Recently a patient cured with Rituximab, an anti CD20 monoclonal antibody, has been reported.[26]

In conclusion, a chronic bronchiolitis with a severe lung function alteration may be the first manifestation of a Sjögren's syndrome. Physicians must be aware on this specific involvement of the bronchial tree as a treatment with macrolides, inhaled corticosteroids and inhaled bronchodilatators, may strongly improve the respiratory status of these patients.

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Conflict of interest

None.

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